Remarks

I. Addressing The Examiner's Objections.

1. Priority.

In the Office action, dated 19 June 2006, the Examiner requested that applicants update the priority information. In this paper, applicants amend the specification to update the priority information as requested by the Examiner.

2. The Declaration.

In the Office action, dated 19 June 2006, the Examiner objected to the oath/declaration asserting that the declaration was defective for the following reasons:

> The oath or declaration is defective because the signatures of the inventors are so light that they are not legible. (Office action, dated 19 June 2006, page 3.)

In a telephone conference with the undersigned on 15 August 2006, the Examiner agreed to reconsider the objection to the specification as the declaration in question was accepted in the parent application. Applicants thank the Examiner for reconsideration of this objection.

3. Figure 3.

In the Office action, dated 19 June 2006, the Examiner objected to Figure 3, under 37 C.F.R. 1.83(a) asserting that it fails to show any details as described in the specification. In a telephone conference with the Examiner on 15 August 2006, applicants confirmed to the Examiner that the original color photograph of Figure 3, illustrating the indirect immunofluorescent staining of adenovirus- and mock-infected cells, was available and would be submitted with applicants response. In accordance with 37 CFR §1.84, accompanying this petition are the following:

> (i) The fee ($130.00) set forth in §1.17(h);
> (ii) Three (3) sets of color drawings; and
> (iii) An amendment to the specification, in the accompanying Response and Amendment, to insert the following language as the first paragraph of the brief description of the drawings: "The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application

publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee."

Also accompanying this petition is a black and white copy of the color Figure 3 to demonstrate that the color drawing is of sufficient quality such that details in the drawings are reproducible in black and white for the printed patent. The black and white copy is stamped "COPY" in blue.

Accordingly, applicants respectfully request that the petition be accepted and that the objection to Figure 3 be withdrawn.

4. Objection to Claims 11 and 14.

The Examiner objected to informalities in claims 11 and 14, asserting the following:

> Claims 11 and 14 are objected to because of the following informalities: the claim recites that the ability of an E1B-55K mutated protein to bind to p53 is reduced when compared to the wild-type E1b-055K [*sic*] protein. For grammatical accuracy, it would be remedial to recite "when compared to the ability of wild-type E1B-55K protein to bind to p53".
>
> Claim 11 is objected to for recitation of "said E1B-55K mutated protein", for accuracy, it would be remedial to recited --said mutated E1B-55K protein--.
>
> As well, claims 11 and 14 are objected to ass [*sic*] recitation of "said treatment" should be --the treatment-- for accuracy.
>
> Appropriate correction is required. (Office action, dated 19 June 2006, page 4.)

In this paper, applicants amend the claims to comply with the Examiner's request. Accordingly, applicants respectfully request withdrawal of the objections to the claims.

II. Addressing The Examiner's Rejections of the Claims.

1. Rejection of Claims 14-19, 23 and 29-32 under 35 U.S.C. §112, First Paragraph.

The Examiner rejected claims 14-19, 23 and 29-32 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, asserting that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the Office action, dated 19 June 2006, the Examiner asserted the following:

> The limitation that the patient is administered "a polynucleotide sequence encoding a recombinant adenovirus" has been added to claim 14 and that the polynucleotide is RNA has been added to claim 15. Applicant has indicated that support for this limitation is found throughout the specification as well as original claim 1. However, the examiner has been unable to find literal support in the originally filed specification or claims for the administration of "a polynucleotide sequence encoding a recombinant adenovirus". The specification does not contemplate administration of a polynucleotide encoding rAd for treatment but teaches infection of patients for delivery of the rAd. Therefore, the limitation is impermissible NEW MATTER. (Emphasis in original, Office action, dated 19 June 2006, pages 4-5.)

In applicants' Response to Restriction Requirement and Amendment, dated 3 April 2006, applicants stated that "the amendments regarding the recombinant adenovirus made to independent claims 11 and 14 correspond to the limitations recited in the issued claims of the parent application (now U.S. Patent No. 6,635,244) of the present application." In the table following this comment applicants noted that the limitations regarding the "recombinant adenovirus" corresponded to the limitations in claim 1 of the allowed parent application (U.S. Patent No. 6,635,244) (see, page 2, subheading 2, Response to Restriction Requirement and Amendment, dated 3 April 2006). Regarding further support for the amendments applicants recited the following:

> Support for the amendments to claims 11 and 14 can be found throughout the specification, for example, at the following locations: page 3, line 31, to page 4, line 9; page 6, lines 11-13; page 6, line 14, to page 7, line 2; page 12, lines 10-20; and Examples 1-3. (See, page 3, first full paragraph, Response to Restriction Requirement and Amendment, dated 3 April 2006.)

Further, applicants note that original claims 14 and 15 of the application as filed were as follows:

> 14. A method of treating cancer in a patient in need of said treatment, comprising administering to said patient a dose of **an isolated polynucleotide wherein said polynucleotide comprises mutated adenoviral DNA that encodes an E1B-55K protein**, said protein comprising a single amino acid mutation which mutation substantially reduces the capacity of said protein to bind to the tumor suppressor, p53, and repeating said treatment if desired.
>
> 15. A method of treating cancer as described in claim 14, wherein said polynucleotide is **RNA**. (Emphasis added, specification, page 26.)

Although the language of the claims might not be considered by the Examiner to be an *ipsis verbis* recitation of "a polynucleotide sequence encoding a recombinant adenovirus," applicants submit that it is clear from the specification that the recombinant adenoviruses of the present invention clearly comprise polynucleotides encoding mutated adenoviral DNA that encodes an E1B-55K protein. It is well settled that "the invention claimed [in the later application] does not have to be described [in the parent] in *ipsis verbis* in order to satisfy the description requirement of §112." *Wagoner v. Barger*, 463 F.2d 1377, 175 USPQ 85 (C.C.P.A. 1972).

In addition, the specification recites the following:

> Adenoviruses of the invention, or the DNA contained therein, may be delivered to neoplastic cells by liposome or immunoliposome delivery; such delivery may be selectively targeted to neoplastic cells on the basis of a cell surface property present on the neoplastic cell population (e.g., the presence of a cell surface protein which binds an immunoglobulin in an immunoliposome). (Specification, page 16, lines 14-17.)

Accordingly, applicants submit that the specification explicitly contemplates use of a polynucleotide (e.g., DNA) comprising the adenoviral mutants described in the present specification for administration to a patient for treatment of cancer. Further, applicants submit that one of ordinary skill in the art would understand the applicants to be in possession of the polynucleotide sequences of the adenoviral mutants in view of the teachings of the specification set forth herein above, as well as, for example, original claims 9 and 10 of the present application:

> 9. An isolated polynucleotide wherein said polynucleotide comprises mutated adenoviral DNA that encodes a E1B-55K protein, said protein comprising a single amino acid mutation which mutation substantially reduces the capacity of said protein to bind to the tumor suppressor, p53.
>
> 10. An isolated polynucleotide as described in claim 9, wherein said polynucleotide is RNA. (Specification, page 25.)

If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 37 USPQ 2d 1578, 1584 (Fed. Cir. 1996).

Accordingly, in view of the above arguments, applicants submit that the claims

comply with the written description requirements of 35 U.S.C. §112, first paragraph, and respectfully request that the rejection of the claims be withdrawn.

2. Rejection of Claims 11, 13-19 and 23-32 under 35 U.S.C. §112, First Paragraph.

The Examiner has rejected claims 11, 13-19 and 23-32 under 35 U.S.C. §112, first paragraph, asserting that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with the claims.

The Examiner objected to claim 12 as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

In the Office action, dated 19 June 2006, the Examiner asserted the following:

> Claims 11, 13-19 and 23-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for treatment of cancer characterized by p53 loss or deficiency by direct administration of a replication competent rAd to a tumor, does not reasonably provide enablement for treating any type of cancer in a human using a recombinant adenovirus comprising a single amino acid mutation in the E1B-55K gene and any other embodiments than replication competent using any other embodiments of administration other than direct administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. (Office action, dated 19 June 2006, page 5.)

Applicants respectfully disagree with the Examiner's assessment of the scope of enablement of the claims, in particular, regarding the route of delivery. Clinical trials are and have been conducted using, for example, intra-arterial administration of a replication-selective adenovirus in patients with colorectal carcinoma metastatic to the liver and intravenous infusion of a replication-selective adenovirus in patients with metastatic solid tumors. Such trials have upheld the safety, feasibility, and biological activity of adenovirus treatment of a number of cancer types. However, in an effort to facilitate prosecution, applicants amend the claims, herein, following the suggestions of the Examiner.

There are two groupings of amended claims, accompanying this paper, as follows: (i) direct administration to a tumor, wherein the tumor cells are characterized by a substantial

lack of p53 function, and (ii) cancer treatment comprising chemotherapy and administering adenovirus. These two groups of claims correspond, respectively, to (i) the Examiner's statement that the specification is enabling "for treatment of cancer characterized by p53 loss or deficiency by direct administration," and (ii) the Examiner's statement that claim 12 was objected to as being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims (Office action, dated 19 June 2006, page 10). Further, each of these two groupings have claims (a) comprising administration of recombinant adenovirus, and (b) comprising administration of a polynucleotide encoding recombinant adenovirus. These groupings correspond to the numbered claims as follows:

> (i)(a) direct administration to a tumor, wherein the tumor cells are characterized by a substantial lack of p53 function, comprising administration of recombinant adenovirus; claims 33-40;
>
> (i)(b) direct administration to a tumor, wherein the tumor cells are characterized by a substantial lack of p53 function, comprising administration of a polynucleotide encoding recombinant adenovirus; claims 41-47;
>
> (ii)(a) cancer treatment comprising chemotherapy and comprising administering adenovirus, comprising administration of recombinant adenovirus; claims 11-13, 24-28; and
>
> (ii)(b) cancer treatment comprising chemotherapy and comprising administering adenovirus, comprising administration of a polynucleotide encoding recombinant adenovirus; claims 14, 16, 17, 29-32.

Amendment or cancellation of the claims is not intended to be an acquiescence in the Office's assessment of those claims in the 19 June 2006 Office action. Applicants expressly reserve the right to bring the subject matter of the original claims again in a subsequent, related application.

In view of the above arguments and amendments, applicants submit that the claims comply with the requirements of 35 U.S.C. §112, first paragraph, and that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled, if necessary, with information known in the art without undue experimentation.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

Gregory Giotta, Ph.D., Esq.
(Reg. No. 32,028)
ONYX Pharmaceuticals, Inc.
2100 Powell Street
Emeryville, CA 94608
Phone: (510) 597-6502
Facsimile: (510) 597-6610.

If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502.

Respectfully submitted,

Date: 19 Sept 2006 By: Gary R Fabian

Gary R. Fabian, Ph.D.
Registration No. 33,875
Agent for Applicants